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Attorney Docket No. OPHD-06331

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: John A. Kink

Serial No.: 09/832,233

Art Unit: 1617

Filed: 04/10/2001

Examiner: Sharareh, S.

Entitled:

Prevention and Treatment of Necrotizing Enterocolitis

**APPELLANTS BRIEF (SUBSTITUTE)
APPEAL NO.:
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By: 

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Sir or Madam:

Enclosed please find a Substitute Appellants Brief, in triplicate, relating to the above referenced patent application. Also enclosed is a petition for an extension of time of two months and a check in the amount of **\$500.00** to cover the cost for filing a response within the second month.

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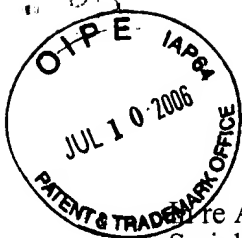
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re Application of: John A. Kink

Serial No.: 09/832,233

Filed: 04/10/2001

Entitled: Prevention And Treatment of Necrotizing Enterocolitis

Group No.: 1617

Examiner: Sharareh, S.

APPELLANTS BRIEF (SUBSTITUTE)

APPEAL NO.:

ATTENTION: Board of Patent Appeals and Interferences
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July 6, 2006	By <u>Traci E. Light</u> Traci E. Light

Sir/Madam:

This Substitute Brief is in response to the Board Of Patent Appeals and Interferences "Order Returning Undocketed Appeal To Examiner" for an alleged lack of compliance to 37 § 41.37(c) having a mailing date of April 6, 2006¹ and is in furtherance of the Notice Of Appeal mailed on November 23, 2004. The Board's Order indicates that the pending brief is missing: i) "Summary of claimed subject matter" as set forth in 37 CFR § 41.37(c)(1)(v); ii) "Grounds of rejection to be reviewed on appeal" as set forth in 37 CFR § 41.37(c)(1)(vi); iii) "Argument" as set forth in 37 CFR § 41.37(c)(1)(vii); iv) "Evidence appendix" as set forth in 37 CFR § 41.37(c)(1)(ix); and v) "Related proceedings appendix" as set forth in 37 CFR § 41.37(c)(x).

The fees required under § 1.17(c) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This Brief is transmitted in triplicate. [37 CFR § 1.192(a).]

¹This Order was not received by the Applicants until June 5, 2006. The Applicants protest the untimely handling of this correspondence by the Office. The Applicants respectfully request that the fee associated with the attached Petition For A Two Month Extension Of Time be reimbursed.

This Brief contains these items under the following headings and in the order set forth below [37 CFR § 1.192(c)]:

I.	REAL PARTY IN INTEREST	4
II.	RELATED APPEALS AND INTERFERENCES	4
III.	STATUS OF CLAIMS	4
IV.	STATUS OF AMENDMENTS	5
V.	SUMMARY OF THE CLAIMED SUBJECT MATTER	6
VI.	GROUND OF REJECTION TO BE REVIEWED UPON APPEAL	6
VII.	ARGUMENT	7
	A. The Examiner Has Failed To Make A <i>Prima Facie</i> Case Of Obviousness	7
	B. Claims 1-5 & 7-14 Are Not <i>Prima Facie</i> Obvious	7
	C. The <i>Prima Facie</i> Standards Of Obviousness	8
	D. The References Do Not Teach "An Anti-TNF Antibody" For Treating Necrotizing Enterocolitis	9
	E. The References Provide No Motivation To Combine	11
	F. The References Do Not Teach Reasonable Success	12
	G. Conclusion	14
VIII.	CLAIMS APPENDIX	i

IX.	EVIDENCE APPENDIX	iii
X.	RELATED PROCEEDINGS APPENDIX	iv

I. REAL PARTY IN INTEREST

The real party in interest is Promega Corporation, 2800 Woods Hollow Road, Madison WI 53711-5399.

II. RELATED APPEALS AND INTERFERENCES

There are no related applications pending appeal.

III. STATUS OF CLAIMS

1. (Appealed) A method of treatment for necrotizing enterocolitis, comprising:
 - a) providing:
 - i) a human neonate, wherein said human neonate has symptoms of necrotizing enterocolitis;
 - ii) a therapeutic formulation comprising purified avian anti-TNF polyclonal antibodies, and;
 - b) administering said formulation to said human neonate.
2. (Appealed) The method of Claim 1, wherein said administering is performed intravenously.
3. (Appealed) The method of Claim 1, wherein said administering is performed orally.
4. (Appealed) The method of Claim 1, wherein said administering is performed parenterally.
5. (Appealed) The method of Claim 1, wherein said administering is performed rectally.
6. (Canceled)

7. (Appealed) The method of Claim 1, wherein said polyclonal avian antibody comprises chicken antibody.
8. (Appealed) The method of Claim 7, wherein said chicken antibody is derived from chicken eggs.
9. (Appealed) A method of treatment for necrotizing enterocolitis, comprising:
- a) providing:
 - i) a neonate at risk for necrotizing enterocolitis,
 - ii) a therapeutic formulation comprising purified avian anti-TNF polyclonal antibody, and;
 - b) administering said formulation to the lumen of the intestine of said neonate.
10. (Appealed) The method of Claim 9, wherein said neonate is a low birth weight neonate.
11. (Appealed) The method of Claim 9, wherein said administering reduces said symptoms.
12. (Appealed) The method of Claim 9, wherein said administering is performed orally.
13. (Appealed) The method of Claim 9, wherein said administering is performed parenterally.
14. (Appealed) The method of Claim 9, wherein said administering is performed rectally.

IV. STATUS OF AMENDMENTS

All amendments in the case have been entered.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Each claim stands alone. Each claim has distinct limitations and must be considered independently.

The first independent claim (Claim 1) recites a method for treating necrotizing enterocolitis (pg 7 ln 26-27) providing a human neonate (pg 10 ln 10; pg 5 ln 17) and purified avian anti-TNF polyclonal antibodies (pg 13 ln 11 - pg 14 ln 3) and administering the antibodies to the neonate (pg 8 ln 1-4). The antibodies may be administered intravenously (pg 9 ln 3). The antibodies may be administered orally (pg 9 ln 3). The antibodies may be administered parenterally (pg 9 ln 3). The antibodies may be administered rectally (pg 9 ln 3). Further, the polyclonal avian antibody may be a chicken antibody (pg 12 ln 21). The chicken antibody may be derived from chicken eggs (pg 12 ln 21).

The second independent claim (Claim 9) also contemplates a method for treating necrotizing enterocolitis (pg 7 ln 26-27) providing a human neonate (pg 10 ln 10; pg 5 ln 17) and purified avian anti-TNF polyclonal antibodies (pg 13 ln 11 - pg 14 ln 3) and administering the antibodies into the intestinal lumen of the neonate (pg 5 ln 23 - pg 6 ln 5). The neonate may be a low birth weight neonate (pg 5 ln 16-22). The antibodies may reduce necrotizing enterocolitis symptoms (pg 7 ln 14-19; pg 5 ln 10-14). The antibodies may be administered orally (pg 9 ln 3). The antibodies may be administered parenterally (pg 9 ln 3). The antibodies may be administered rectally (pg 9 ln 3).

VI. GROUNDS OF REJECTION TO BE REVIEWED UPON APPEAL

Claims 1-5 and 7-14 stand rejected under 35 U.S.C. § 103(a) as unpatentably under US Pat. No. 5,656,272 To Le et al. or US Pat. No. 5,833,984 To Eibl et al. ("Eibl II") in view of Wolf et al. *Acta Pediatr. (supp)* 396:37-40 (1994), Muguruma et al., *Prenat. Neonat. Med.* 3:571-579 (1998); "Eibl I" *Acta Pediat* 83:666-668 (1994), and US Pat No. 5,601,823 To Williams et al.

VII. ARGUMENT

A. The Examiner Has Failed To Make A *Prima Facie* Case Of Obviousness

The Examiner fails to make a *prima facie* case of obviousness because the asserted reference combination does not: i) disclose all of the claim limitations; ii) offer any motivation for the combination; and iii) teach any reasonable expectation of success.

In the last Office Action Response, the Applicants successfully overcame an obviousness rejection based upon Ebil II as the primary reference, in view of Muguruma *et al.*, Eibl I, and Wolf *et al.* The Applicants submit that the Examiner has added the Le *et al.* reference which has the same admitted deficiencies as Ebil II. The Examiner, therefore, has unnecessarily continued the pending examination by re-presenting the same unsupported argument using a different set of references.

Further, in the present rejection (*i.e.*, *Second Final Office Action*), the Examiner increases the number of cited references from four (4) to six (6) by adding Le *et al.* (US Pat. No. 5,656,272) as an alternative primary reference and, Williams *et al.* (US Pat. No. 5,601,823) as an additional secondary reference.²

B. Claims 1-5 & 7-14 Are Not *Prima Facie* Obvious

The Examiner has not properly established the *prima facie* obviousness of the rejected claims. For example, the Examiner makes the conclusory statement:

The role of TNF as a pro-inflammatory mediator in development of NEC has been well established in the art as shown by Muguruma, Wolf and Eibl I. Therefore, even though Le does not explicitly disclose the use of anti-TNF antibodies in treating NEC in neonates, it would have been obvious to one of ordinary skill in the art at the time of invention to employ such products for treatment of NEC, because as suggested by Eibl II, Muguruma and Eibl I and Wolf, TNF plays an integral role in development of NEC and the ordinary skill in the art would have had a reasonable expectation of success in employing the anti-TNF of Le for treating NEC. Furthermore, one of ordinary skill in the art would have been motivated to formulate an avian polyclonal anti-TNF, because as suggested by Williams such type of antibodies can be administered orally, are non-immunogenic and are well tolerated by infants. *Second Final Office Action* 07/01/04 pg. 3.

² The Board is reminded that the Federal Circuit views an ever increasing number of cited references to support a 103(a) rejection as an indicator of non-obviousness.

The Applicants disagree because the Examiner's statements are: i) unsupported, improper, and contain bald conclusions without a factual basis; and ii) do not meet the proper standards to establish a *prima facie* case of obviousness.

C. The *Prima Facie* Standards Of Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A *Prima Facie* Case Of Obviousness. The Examiner is reminded that if ONLY ONE of the above requirements is not met, then a *prima facie* case of obviousness does not exist. The Applicants submit that the Examiner's rejection does not meet these criterion.

As a preliminary matter, when dealing with a rejection based upon obviousness it is essential for the Examiner to view the claimed embodiment as a whole:

[T]he question under 35 U.S.C. § 103 is not whether the differences *themselves* would have been obvious. Consideration of differences, like each of the findings set forth in *Graham*, is but an aid in reaching the ultimate determination of whether the claimed invention *as a whole* would have been obvious.

Stratoflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1537, 218 USPQ 871 (Fed. Cir. 1983) (emphasis in the original). It is clear to the Applicants that the Examiner has not "stepped back" from the elements to actually "see" the claimed embodiment. Specifically, the Examiner creates the obviousness rejections by "picking and choosing" specific elements among the cited publications and subsequently uses the specification in hindsight.³ The Federal Circuit has noted that: "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992). The Applicants note that the

³ A practice not permitted under patent law. See, *In re Rouffet*, 149 F.3d 1350, 47 USPQ.2d 1453 (Fed. Cir. 1998); and *In re Warner*, 379 F.2d 1011, 154 USPQ 173 (CCPA 1967).

Examiner's conclusions allegedly establishing a *prima facie* case of obviousness are not supported by cited reference quotations.

D. The References Do Not Teach "An Anti-TNF Antibody" For Treating Necrotizing Enterocolitis

The Examiner admits that *Le et al.* (US Pat. No. 5,656,272) does not teach an anti-TNF antibody: "Le fails to specifically teach anti-TNF use for treating Neonatal Necrotizing Enterocolitis (NEC)." *Second Final Office Action*, pg. 2. The Applicants submit that *Le et al.* also fails to properly disclose NEC. Even if *Le et al.* did mention necrotizing enterocolitis (which it does not) this would only be an "invitation to try", a rejection basis also forbidden by the Federal Circuit.⁴

The Examiner admits that *Ebil II* (US Pat. No. 5,833,984) does not teach an anti-TNF antibody: "Eibl fails to specifically use anti-TNF antibodies in treating NEC." *Second Final Office Action*, pg. 2. Instead of advocating that necrotizing enterocolitis should be treated by specific anti-TNF antibodies, *Ebil II* teaches TNF- α release inhibition by IgA multimer complexes that also sequester circulating TNF- α :

... human serum IgA, which is largely monomeric, inhibits monocyte cytokine release. Heat aggregation, which forms IgA multimers, enhances the inhibitory effect of IgA on TNF- α release.

Ebil II, col 7 ln 66 - col 8 ln 2. *Ebil II*, therefore, teaches that necrotizing enterocolitis immunotherapy does not involve direct neutralization by specific antibodies (*i.e.*, for example, anti-TNF antibody).

The Examiner admits that *Wolf et al.* (Acta Pediatr Suppl 396:37-40 (1994)) does not teach anti-TNF antibody: "Wolf, for example, describes the general knowledge about the effects of oral IgA-IgG preparations ..." *Second Final Office Action*, pg. 3. Even if *Wolf et al.* disclosed anti-TNF antibody (which it does not), *Wolf et al.* provides support for the hypothesis that immunotherapy inhibits the release of TNF- α :

⁴ "An invention is 'obvious to try' 'where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful.'" *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988).

The purpose of the present study was to investigate whether the oral IgA-IgG preparation used for prophylaxis of NEC might have regulatory effect on the release of inflammatory cytokines like TNF alpha and IL-6 by human monocytes.

Wolf et al., pg.38 rhc. *Wolf et al.*, therefore, teaches that necrotizing enterocolitis immunotherapy does not involve direct neutralization by specific antibodies (*i.e.*, for example, anti-TNF antibody).

The Examiner admits that Eibl I (NEJM 319:1-7 (1988)) does not teach anti-TNF antibody: "Eibl I sets forth successful use of IgA-IgG ..." *Second Final Office Action*, pg. 3. Not only is Eibl I silent on anti-TNF antibody, Eibl I is also silent on TNF- α .

The Examiner admits that Muguruma *et al.* (Prenat Neonate Med 3:571-579 (1998)) does not teach anti-TNF antibody: "Muguruma *et al.*, however, fails to specifically teach the use of antibodies ..." *Second Final Office Action*, pg. 3. Even if Muguruma *et al.* disclosed anti-TNF antibody (which it does not), Muguruma *et al.* provides evidence that TNF- α may not directly cause necrotizing enterocolitis:

Although we were successful in producing a full thickness hemorrhage by the treatment with these agents [TNF- α & LPS], a clearly identifiable necrosis was not evident (Tables 2 and 3).

Muguruma et al., pg. 578 lhc. The Board must recognize that Muguruma *et al.* does not disclose anti-TNF antibodies and casts doubt on whether or not TNF- α is directly responsible for necrotizing enterocolitis.

The Examiner admits that Williams *et al.* (US Pat. No. 5,601,823) does not teach anti-TNF antibody: "Williams is merely used to show the state of the art in formulating polyclonal avian antibodies for treating inflammatory enterocolitis caused by *Clostridium difficile*." *Second Final Office Action*, pg. 3. Not only is Williams *et al.* silent on anti-TNF antibody, Williams *et al.* is also silent on TNF- α .

It is easily seen that the Examiner has not offered a single reference that discloses an anti-TNF antibody used for treating necrotizing enterocolitis. Consequently, on this fact alone, the obviousness rejection fails.

E. The References Provide No Motivation To Combine

As detailed above, the Examiner's belief that the cited references teach the use of anti-TNF antibodies for treatment of NEC is simply wrong. The Examiner has pointed to no statement in any reference that suggests an antibody to a TNF antigen would be useful to treat NEC. The Applicants point out that Ebil II provides teachings regarding IgA that are contrary to the teachings in both Wolf *et al.* and Ebil I⁵, for example:

... IgG appears to actually enhance inflammatory activity, which is undesirable. Accordingly, it is preferred to use IgA which is essentially free of IgG.

Ebil II, col 6 ln 31-34. Ebil II also teaches away from the Applicants' claimed embodiment by disclosing that a non-specific antigen/antibody interaction is the preferred approach to immunoprotection against necrotizing enterocolitis:

This effect [when using IgA/IgG] is believed to be a result of the formation of antigen-antibody **complexes** caused by high titers of antibodies against a multitude of potential pathogens and their toxins.

Ebil II, col 2 ln 24-27 [emphasis added]. Clearly, the Examiner's assumption that an unstimulated crude fractionated IgA-IgG plasma preparation is equivalent to anti-TNF antibody (as described in the Applicants' specification) demonstrates a basic misunderstanding of Applicants' claimed embodiment and is contrary to level of skill in the art.

The Applicants conclude, therefore, that the Examiner cannot point to any statement in the combination of Le *et al.*, Eibl II, Muguruma *et al.*, Eibl I, Wolf *et al.*, or Williams *et al.* that suggests or motivates one skilled in the art to generate an anti-TNF antibody to treat NEC. The Examiner has failed to indicate where in the references cited there is such a suggestion of desirability to combine. The Examiner must provide a basis for combining art prior to considering the combination. Indeed, the requirement that the Examiner make a showing of a suggestion, teaching or motivation to combine the prior art references is "an essential evidentiary component of an obviousness holding." *C.R. Bard, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998). There are three sources for this evidentiary component: the prior art references

⁵ Both Wolf *et al.* and Ebil I teach IgA/IgG combinations.

themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996). The suggestion most often comes from the teachings of the pertinent references. *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998). Nonetheless, regardless of the source of the requisite evidence, the Examiner's showing "must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not 'evidence'." *In re Dembiczak*, 175 F.3d 994, 1000 (Fed. Cir. 1999).

Instead, the Examiner presupposes to be "one skilled in the art". The Examiner is reminded that - under the law - an Examiner is NOT one skilled in the art; mere opinion of the Examiner on what one skilled in the art might believe does not count. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) ("[T]he examiner's assumptions do not constitute the disclosure of the prior art.").

The Examiner has the burden of showing that the cited art is justified by "evidence" which supplies a suggestion, teaching or motivation sufficient to provide one skilled in the art to create the Applicant's invention.

Looking at the cited references themselves, there are no objective teachings that would lead that individual to create the Applicant's invention. Indeed, the Examiner points to nothing in the references themselves which teach or suggest the invention. In this manner, the Examiner has not satisfied his burden under the law. *See In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)("[W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears.").

Because there are no suggestions or motivations within the cited references to support the Examiner's combination, the rejection fails.

F. The References Do Not Teach Reasonable Success

The Examiner attempts to establish this prong of *prima facie* obviousness by stating:

... it is well established that TNF potentiates the progress of NEC and thus reducing the effects of TNF activity among human infants would improve or alleviate the pathological changes that would lead to NEC. Examiner states that any degree of relief for NEC would read on the scope of the instant claims, and the ordinary skill in the art would have

had a **reasonable expectation of success** in at least observing some symptomatic relief when administering the anti-TNF **taught by Eibl**.

Second Final Office Action, pg. 4 [emphasis added]. At the outset, the Applicants reiterate that the Examiner's statement that Eibl II teaches NEC treatment by anti-TNF is erroneous (*supra*). Further, the Federal Circuit requires any reference asserted for an "expectation of success" to explicitly predict that the recited claims will work. *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). Consequently, it is the Examiner who is making the conclusions that "reducing the effects of TNF activity among human infants would improve or alleviate ... NEC", **not** "one having ordinary skill in the art". As asserted above, the Examiner is continuing to speculate without a factual basis.

One example regarding the Examiner's lack of facts is that three (3) of the asserted references (Eibl II, Wolf *et al.*, and Eibl I)⁶ all teach preparations of IgA and/or IgG that are merely fractionated plasma extractions:

Preferably, a plasma fraction is used as a source of IgA. For example, an IgA fraction can be obtained by ion exchange chromatography, hydrophobic chromatography, hydrophilic chromatography or affinity chromatography of a plasma fraction ...

Eibl II, col 8 ln 10-14. The Board is reminded that the production of specific anti-TNF antibodies require immunization procedures. TNF immunization is not taught by these references and, therefore, these references cannot explicitly predict the success of using anti-TNF antibodies.

Additionally, the Examiner has misconstrued the pending claims by stating that: "... any degree of relief for NEC would read on the scope of the instant claims ..." (*supra*). The Examiner has erroneously concluded that these claims encompass reduced TNF activity by any means.

This rejection must fail because when the cited references fail to disclose a specific claim element (*supra*) the references clearly cannot explicitly predict the claim's success.

⁶ These three cited references share common inventors and disclose the same technology.

G. Conclusion

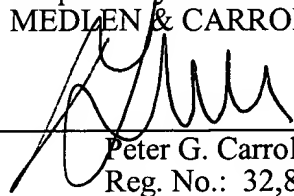
Appellants submit that, with due consideration to all these factors discussed above, the patentability of Claims 1-5 and 7-14 is evident. The standards regarding a *prima facie* case of obviousness are not met against the Examiner's cited references. Consequently, the rejection fails.

For the foregoing reasons, it is submitted that the examiner's rejection of Claims 1-5 and 7-14 was erroneous, and reversal of this rejection is respectfully requested.

Respectfully submitted,
MEDLEN & CARROLL, LLP

Dated: July 6, 2006

By: _____



Peter G. Carroll
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Attorneys for Appellant

VIII. CLAIMS APPENDIX



PATENT
Attorney Docket No. **OPHD-06331**

1. A method of treatment for necrotizing enterocolitis, comprising:
 - a) providing:
 - i) a human neonate, wherein said human neonate has symptoms of necrotizing enterocolitis;
 - ii) a therapeutic formulation comprising purified avian anti-TNF polyclonal antibodies, and;
 - b) administering said formulation to said human neonate.
2. The method of Claim 1, wherein said administering is performed intravenously.
3. The method of Claim 1, wherein said administering is performed orally.
4. The method of Claim 1, wherein said administering is performed parenterally.
5. The method of Claim 1, wherein said administering is performed rectally.
7. The method of Claim 1, wherein said polyclonal avian antibody comprises chicken antibody.
8. The method of Claim 7, wherein said chicken antibody is derived from chicken eggs.
9. A method of treatment for necrotizing enterocolitis, comprising:
 - a) providing:
 - i) a neonate at risk for necrotizing enterocolitis,

- ii) a therapeutic formulation comprising purified avian anti-TNF polyclonal antibody, and;
 - b) administering said formulation to the lumen of the intestine of said neonate.
-
- 10. The method of Claim 9, wherein said neonate is a low birth weight neonate.
 - 11. The method of Claim 9, wherein said administering reduces said symptoms.
 - 12. The method of Claim 9, wherein said administering is performed orally.
 - 13. The method of Claim 9, wherein said administering is performed parenterally.
 - 14. The method of Claim 9, wherein said administering is performed rectally.

IX. EVIDENCE APPENDIX

There is no Evidence Appendix presented in this appeal.

X. RELATED PROCEEDINGS APPENDIX

There is no Related Proceedings Appendix presented in this appeal.

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